Nature, Volume 377 (6457 suppl.) pp 3-174. Consequently, Adams, *et al.* is prior art under 35 U.S.C.§ 102(b) and that when assigning effective filing dates to claims, each claim is considered as a whole.

Applicant will clarify. Base pair position 14-482 of SEQ ID NO. 4 in the instant application correlates with parent SEQ ID NO. 4 in its entirety. The claims originally filed in this application, as amended, claim 14-482 of instant SEQ ID NO. 4 and, therefore, entitled to the parent priority (i.e. October 31, 1996). New claim 49 covers instant SEQ ID NO. 4 in its entirety and is entitled the instant filing date.

SEQ ID NO. 5 is not found in parent case and is also included in new claim 49, which is entitled to the instant filing date. SEQ ID NO. 5 has been deleted from claims other than Claim 49.

Claims 1-10, 35 and 40-42 are rejected under 35 U.S.C. § 112, first paragraph because the claims have been amended to recite that the method is for detecting the presence of a polynucleotide indicative of breast disease by probing with a polynucleotide has 90% identity with SEQ ID NO. 5 and detecting the presence of the target polynucleotide indicative of breast disease. The Examiner concludes stating that the data presented in the specification does not associate breast disease with this marker.

Applicant respectfully, yet vigorously disagrees. The probe used in the Northern analysis is not SEQ ID NO 1, rather it is the complement of that sequence prepared as described on p 62 lines 20-23. The Examiner accurately summarizes the results of Example 5, a Northern Blot Analysis, as displayed in Figures 3A and 3B. However, the results in Table 1 are not from a Northern Blot analysis, but rather are the result of a Ribonuclease Protection Assay as described in detail in Example 4. The tissue samples used in the two assays are not the same; hence identical results are not to be expected. Furthermore, the examiner has not considered the results of Example 8, an RT-PCR analysis of tumor and normal specimens, in drawing the conclusion that "the teachings in the specification are limited and do not allow the skilled artisan to draw a reasonable and predictable conclusion as to an association with breast cancer, ...". On the contrary, the inventors have demonstrated in the examples of the patent application that BS106 meets the criteria of being a major tumor marker such as Prostate Tumor Antigen (PSA) or the recently discovered Mammaglobin.

For a gene or gene product such as mRNA or protein to be useful as a disease maker when it is expressed in normal tissue (as are PSA and mRNA), it is necessary that

either the distribution of the gene product or the abundance of the gene product is altered in the disease state. In the case of PSA, it is present in the normal prostate, and it's concentration does not rise in disease; however, in the case of prostate cancer, frequently PSA leaks into the peripheral circulation where it is detected as an increase in concentration of PSA in serum. Alternatively, prostate cells which express mRNA for PSA may leak into circulation where they can be detected by amplification methods such as RT_PCR. US patent 5,506,106 by Croce et al, describe such a test and the results in which 4 of 12 prostate cancer patients had circulating PSA mRNA in their blood. Furthermore, in advanced, hormone independent prostate cancer, the secretion of PSA may cease, and the blood level of PSA protein or mRNA may go to zero. Also, tissue biopsies of hormone independent advanced prostate cancer show reduced or no expression of PSA in immunohistochemistry.

The new breast specific molecule, Mammaglobin, is found exclusively in breast tissue as reported by Watson et al in US patent 6004756 and Cancer Research, 56, 860-865 (1996). Northern Blot analysis finds Mammaglobin over expressed in 4 of 15 breast cancers according to US6004756, and in 8 of 35 breast cancers in Cancer Research. It is not found in any normal tissue besides breast. Furthermore it is apparently not expressed at a level detectable by Northern Blot analysis in some breast cancers. In Fig 5B of the Cancer Research paper, 2 of 6 breast cancers appear to express no Mammaglobin.

Therefore, it is seen that for well known tumor markers, including the new breast cancer marker, Mammaglobin, the pattern of expression is similar to that seen with BS 106. BS106 is found in 8 of 9 normal breast samples analyzed by Northern Blot (Example 5), and in 6 of 6 normal breast samples analyzed by the more sensitive Ribonuclease Protection Assay (Example 4) and in 5 of 5 normal breast samples analyzed by the even more sensitive RT-PCR assay (Example 8). The only non-breast tissue in which BS106 RNA is found is prostate cancer which should not present a specificity problem with breast cancer. Therefore, if a BS106 gene product (RNA or protein) is found in a non-breast compartment, for example blood or lymph node, it is highly likely that a proliferative breast disease or a disease which disrupts the normal tissue architecture of the breast is present in the patient.

Furthermore, considering the quantity of RNA in tumor tissue, it is apparent from the quantitative results in Example 4 that some tumors (2 of 6) upregulate BS106 RNA relative to normal tissue, some have normal levels(1 of 6) and some have essentially zero

(3 of 6). This is similar to observations for Mammaglobin in breast cancer as well as better characterized markers of breast cancer such as HER-2/neu (US Patent 4,968,603 by Slamon and McGuire) in which a fraction of tumors overexpress the marker, others have normal levels, and some have essentially none, either due to deletion or rearrangement of the gene.

Finally, the Examiner states, "the specification has not provided any guidance with regard to the presence of (sic) absence of a genomic DNA sequence which hybridizes with SEQ ID NO 1-5...". Example 8, figure 4A and 4B both included a large amount of placental DNA which gives no BS106 specific signal. It is inherent from the data that the gene of BS106 has one or more introns which prevent the mRNA-derived probes from binding to the genomic DNA which might be present in the samples in spite of the extraction which seeks to minimize DNA in the sample for analysis. Based on the aforementioned, it is respectfully requested that this ejection be withdrawn.

CONCLUSION

In view of the aforementioned amendments and remarks, the aforementioned application is in condition for allowance and Applicant requests that the Examiner withdraw all outstanding objections and rejections and to pass this application to allowance.

Respectfully submitted,

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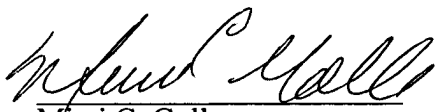

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